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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/091,500	03/07/2002	Yusuke Amino	217637US0CONT	8895

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EXAMINER

ZUCKER, PAUL A

ART UNIT	PAPER NUMBER
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1621

DATE MAILED: 09/09/2002

6

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/091,500

Applicant(s)

AMINO ET AL.

Examiner

Paul A. Zucker

Art Unit

1621

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-39 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-39 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>4</u> . | 6) <input type="checkbox"/> Other: . |

DETAILED ACTION

Specification

1. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.
2. The disclosure is objected to because of the following informalities:
 - a. Applicant should remove the phrase "TITLE OF THE INVENTION" from the top of page 1;
 - b. Applicant should insert the sentence : "This application is a continuation of PCT/JP00/05665 filed August 23, 2000" as the first line of the specification after the title.

Appropriate correction is required.

Claim Objections

3. Claim 25 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim. Claim 25 depends, in a non-alternative way, on both claims 1 and 24. See MPEP § 608.01(n).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 3, 22, 31, 32 and 36-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 3 recites the limitation "N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester comprising". A compound comprises only itself. Claims 3, and it dependent are therefore rendered indefinite.
5. Claims 4, 6, 8-14, 16, 26, 32 and 34-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 4, 6, 8-14, 16, 26, 32 and 34-39 recite the limitation "(s)" (For example, in claim 4, line 2). The use of parenthetical expressions renders the claims indefinite because it is unclear whether the limitation(s) enclosed in parentheses are part of the claimed invention. Applicant is required to correct these and all other errors of this type in the claims. See MPEP § 2173.05(d).
6. Claims 7 and 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 7 and 33 recite the limitation "a solvent which has been used in the reductive alkylation reaction". It is unclear from this recitation whether Applicants intend that the same same solvent used in the reductive alkylation be used in the crystallization or simply that one of the solvents

that has been used in the past be employed. Claims 7 and 33 are therefore rendered indefinite.

7. Claims 1, 2, 3, 5, 6, 8-10, 13, 14, 26, 31- 34, 38 and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims claim the process of crystallization but fail to set forth any specific steps in the process claimed. Claims 1, 2, 3, 5, 6, 8-10, 13, 14, 26, 31- 34, 38 and 39 are therefore rendered indefinite.
8. Claims 1,2, 4- 21, 23, 25 –30 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites the limitation “said compound” in line 6. There is insufficient antecedent basis for this limitation in the claim. Claim 1 and its dependents are therefore rendered indefinite.
9. Claims 15 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 15 and 20 recite the limitation “said reductive alkylation reaction” in lines 1 and 2, respectively. There is insufficient antecedent basis for this limitation in the claims.
10. Claims 8 and 34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter

which applicant regards as the invention. Claims 8 and 34 recite the limitation "aspect" in lines 1 and 2, respectively. There is insufficient antecedent basis for this limitation in the claims.

11. Claims 31 and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant appears to be claiming the process of crystallizing an impurity and not the object of the invention. Claims 31 and 32 are therefore rendered indefinite.

12. Claims 16 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 16, and 22 recite the limitation "3-(3-methoxy-4-protectedhydroxyphenyl)". Applicant has not set forth the protecting groups contemplated. Claims 16 and 22 are therefore rendered indefinite.

13. Claim 24 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 24 recites the limitation "in at least" in line 2. This limitation renders the claim indefinite since it is unclear which peaks are characteristic of the claimed compound.

14. Claim 24 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant

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regards as the invention. Claim 24 recites the limitation "(2 θ , CuK α ray)" in line 2.

This limitation renders the claim indefinite since it is unclear whether peaks are characteristic of the compound claimed. The phrase "(2 θ , CuK α ray)" renders the claim indefinite because it is unclear whether the limitation enclosed within parentheses are part of the claimed invention. See MPEP § 2173.05(d).

15. Claims 1,2,3, 13,14,21 and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1, 2, 3, 13,14, 21 and 39 recite the limitation "Aspartame". Aspartame is a tradename and its use renders the claims indefinite since it is not a proper identification of the substance. Applicant is required to correct these and all other occurrences in the claims.

16. Claim 25 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 25 recites the limitation "can be" in line 1. The phrase "can be" renders the claim indefinite because the claim includes elements not actually disclosed (those encompassed by "can be"), thereby rendering the scope of the claim(s) unascertainable. See MPEP § 2173.05(d).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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17. Claims 1, 2, 3, 5, 6, 8-10, 13, 14, 26, 31- 34, 38 and 39 are rejected under 35

U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. While it is true that the level of ordinary skill in the chemical arts is high, crystallization is well known by those of ordinary skill in the art to be highly solvent dependent. Applicants' recitation of a group of solvents which represent virtually every class of solvent (water, alcohols, ethers, ketones, esters, hydrocarbons, etc., and mixtures thereof) provides little guidance to one of ordinary skill in the art as to which solvent or solvent system to employ. One of ordinary skill in the art could not, therefore, practice the invention without undue experimentation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

18. Claims 1- 6, 8, 9, 13, 14, 16, 19, 21, 22, 31, 32, 34, 35, 38 and 39 are rejected under

35 U.S.C. 103(a) as being unpatentable over Nofre et al (US 5,480,668 01-1996).

Nofre discloses (Column 8, Table 1, entries 18 and 19) the compounds N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester and

its unsaturated counterpart. Nofre further discloses (Column 7, lines 24-51) a general process for its synthesis. Nofre discloses a process for reductive alkylation of aspartame with the appropriate aldehyde (1.099 molar ratio aldehyde/aspartame) in methanol at room temperature for 24 hours. Nofre discloses removal of the reaction solvent (methanol) washing with aqueous HCl (to remove aspartame) and its replacement with ethanol/water as a recrystallization solvent (solvent substitution). Aspartame as well as other impurities, is removed via the disclosed crystallization.

19. Claims 23 -26 are rejected under 35 U.S.C. 102(b) as being anticipated by Nofre et al (US 5,480,668 01-1996). Nofre discloses (Column 8, Table 1, entries 18 and 19 and column 7, lines 24-51) the compounds N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester and its corresponding unsaturated counterpart and their crystallization from alcohol solvent. Compounds are distinguished by their atoms and bonds and not by their method of production. The diffraction peaks are an inherent property of the compound disclosed by Nofre. Claims 23-26 are therefore anticipated by Nofre et al.

20. Claims 27 and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Nofre et al (US 5,480,668 01-1996). Nofre discloses (Column 10, lines 42-47, claims 6 and 7) the use of the instantly claimed compound of N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester as a sweetening

agent in combination with carriers or bulking agents. Claims 27 and 28 are therefore anticipated by Nofre.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

21. Claims 15, 17, 18, 20, 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nofre et al (US 5,480,668 01-1996) as applied to claims 1- 6, 8, 9, 13, 14, 16, 19, 21, 22, 31, 32, 34, 35, 38 and 39 above and further in view of Claude et al (US 5,510,508 04-1996).

Instantly claimed is a method for the production of N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester comprising subjecting 3-(3-methoxy-4-hydroxyphenyl) propionaldehyde and Aspartame to

reductive alkylation via hydrogenation in the presence of a catalyst followed by crystallization.

The difference between the process taught by Nofre and the instant process is that Nofre teaches a process for reductive alkylation which employs sodium cyanoborohydride as a reductant while the instant application claims the use of a catalytic hydrogenation reaction. Additional differences are that Nofre does not indicate the pH of the process

Claude, however, teaches (Column 3, line 63- column 4, line 26) a reductive alkylation reaction between 3,3-dimethylbutyraldehyde and aspartame in methanol solution in the presence of platinum catalyst and hydrogen gas at 1 bar at room temperature. Claude teaches (Column 3, lines 8-11) the use of both palladium and platinum as catalysts. Claude further teaches (Column 3, lines 45-48) reaction at a pH of 4.5-5.

Thus the instantly claimed process would have been obvious to one of ordinary skill in the art. The suggestion to combine is found in the nearly identical fields of invention. The motivation would have been to modify the general process for the synthesis of N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester taught by Nofre by replacing his conditions for reductive alkylation with those taught by Claude. The expectation for success would have been very high based on the fact that one equivalent process was being replaced by another.

22. Claims 7, 10-12, 33 and 36-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nofre et al (US 5,480,668 01-1996) as applied to claims 1- 6, 8, 9, 13, 14, 16, 19, 21, 22, 31, 32, 34, 35, 38 and 39 above and further in view of Prakash et al (US 6,077,962 07-2000).

Instantly claimed is a method for the production of N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester comprising subjecting 3-(3-methoxy-4-hydroxyphenyl) propionaldehyde and Aspartame to reductive alkylation followed by an extractive workup and crystallization. The use of the same solvent for reductive alkylation and crystallization is claimed as well.

The difference between the process taught by Nofre and the instant process is that Nofre prefers crystallization without a previous extractive workup.

Prakash, however, teaches (Column 14, line 48- column 15, line 32) a process for the synthesis of N-neohexyl- α -aspartame (neotame). Prakash further teaches extractive workup of the product neotame using water-ethyl acetate followed by recrystallization from methanol -water. Methanol was used as the solvent for reductive alkylation as taught by Prakash.

Thus the instantly claimed process would have been obvious to one of ordinary skill in the art. The motivation would have been to improve the process taught by Nofre modify using the extractive workup suggested by Prakash. Since the fields of

invention are the same (synthesis of aspartame derivatives) the expectation for success would have been high.

23. Claims 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nofre et al (US 5,480,668 01-1996) and Claude et al (US 5,510,508 04-1996) as applied to claims 1- 6, 8, 9, 13-22, 30-32, 34, 35, 38 and 39 above and further in view of Solomons (Organic Chemistry 1992, John Wiley & Sons, Inc. New York, pages 305-311).

Instantly claimed is a method for the production of N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester comprising subjecting 3-(3-methoxy-4-hydroxyphenyl) propenylaldehyde and Aspartame to reductive alkylation. The simultaneous reduction of the intermediate imine and the double bond in the starting aldehyde is claimed as well.

The difference between the disclosure of Nofre and Claude and the instantly claimed process is that Nofre does not produce N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester via reduction of the double bond in the 3-(3-methoxy-4-hydroxyphenyl) propenylaldehyde but instead uses the reduced aldehyde as starting material. Using 3-(3-methoxy-4-hydroxyphenyl) propenylaldehyde as starting material, however, is obvious in the process of Nofre as modified by the teaching of Claude since Nofre teaches both unsaturated and saturated aldehydes as starting materials. One of ordinary skill in the art would

recognize that when the reductive alkylation was carried out via catalytic hydrogenation instead of sodium cyanoborohydride treatment the double bond in the unsaturated aldehyde would automatically be reduced to give the saturated product.

Solomons teaches (Page 305) the catalytic hydrogenation of alkenes to give the saturated compounds.

Thus the instantly claimed process would have been obvious to one of ordinary skill in the art. The suggestion for combination of the references would have been found in the recognition of the chemistry involved and the motivation would have been to eliminate a synthetic step resulting in an increase in the cost effectiveness of the process for synthesis of commercial sweeteners.

Conclusion

24. Claims 1-39 are outstanding. Claims 1-39 are rejected. Claim 25 is objected to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul A. Zucker whose telephone number is 703-306-0512. The examiner can normally be reached on Monday-Friday 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R. Richter can be reached on 703-308-4532. The fax phone numbers for the organization where this application or proceeding is assigned are

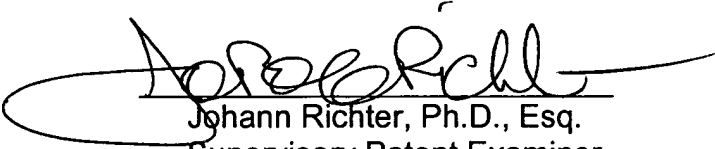
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703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Paul A. Zucker
Patent Examiner
Technology Center 1600

August 29, 2002



Johann Richter, Ph.D., Esq.
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